

Elemental formula associated hypophosphataemic rickets.

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Title: Elemental formula associated hypophosphataemic rickets

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Abstract:

Objectives: Hypophosphataemic rickets (HR) is usually secondary to renal phosphate wasting but may occur secondary to reduced intake or absorption of phosphate. We describe a series of cases of HR associated with the use of Neocate[®], an amino-acid based formula (AAF).

Methods: A retrospective review of cases with HR associated with AAF use presenting to centres across the United Kingdom.

Results: 10 cases were identified, over a 9 month period, all associated with Neocate[®] use. The age at presentation was 5 months to 3 years. The majority (8/10) were born prematurely. Gastro oesophageal reflux disease (6/10) was the most frequent indication for AAF use. Radiologically apparent rickets was observed after a median of 8 months (range 3-15 months) of exclusive Neocate[®] feed. The majority (7/10) were diagnosed on the basis of incidental findings on radiographs: rickets (6/10) or fracture with osteopenia (5/10). All patients had typical biochemical features of HR with low serum phosphate, high alkaline phosphatase, normal serum calcium and 25 hydroxyvitamin D. However, in all cases the tubular reabsorption of phosphate (TRP) was $\geq 96\%$. Phosphate supplementation resulted in normalisation of serum phosphate within 1 to 16 weeks, and levels remained normal only after Neocate[®] cessation. In patients with sufficient follow up duration (4/10), normalisation of phosphate and radiological healing of rickets was noted after 6 months (range: 6- 8 months) following discontinuation of Neocate[®].

Conclusion: The presence of a normal TRP and resolution of hypophosphataemia and rickets following discontinuation of Neocate[®] indicates this is a reversible cause likely mediated by poor phosphate absorption. Close biochemical surveillance is recommended for children on

Neocate[®], especially in those with gastrointestinal co-morbidities, with consideration of a change in feed or phosphate supplementation in affected children.

Introduction:

Rickets is caused by defective mineralisation at the growth plate. Rickets is often classified as calcipenic or phosphopenic depending on whether the primary cause is a shortage of calcium or phosphate. However, the underlying mechanism of all forms of rickets is low phosphate availability at the growth plate preventing apoptosis of hypertrophic chondrocytes and reduced mineralisation of newly formed bone matrix [1]. The leading cause of nutritional rickets worldwide is vitamin D deficiency [2]. Hypophosphataemic rickets (HR) in children usually has an underlying genetic basis [3], but HR may also occur from chronic hypophosphataemia secondary to reduced phosphate availability from poor oral intake or malabsorption or renal phosphate leak. Dietary phosphate deficiency is now a rare entity having previously been seen in premature babies who were exclusively breast milk fed [4]. Poor gastrointestinal phosphate absorption can occur in the setting of prematurity, vitamin D deficiency and use of phosphate binders [5]. Increased renal phosphate loss occurs in primary or secondary hyperparathyroidism, vitamin D deficiency and renal tubular disorders such as Lowe's syndrome, Dent's disease, congenital or acquired Fanconi's syndrome [6].

Renal phosphate wasting is associated with low tubular reabsorption of phosphate (TRP) whereas low serum phosphate from dietary deficiency or malabsorption is associated with a normal or high TRP. Recently, the use of elemental formula was implicated in the development of HR [7]. Here, we describe a series of cases from across the United Kingdom with a rare cause of hypophosphataemia and HR related to the use of an amino acid based formula (AAF), Neocate[®].

Methods:

A retrospective review of case notes was undertaken of children with hypophosphataemia and HR, whilst consuming Neocate[®], a specific AAF, from various centres across the United Kingdom. Following description of the first case of Neocate[®] associated HR in the UK in 2016 [8] an effort was made to identify similar cases through the British Paediatric and Adolescent Bone Group and the British Society of Paediatric Endocrinology and Diabetes monthly newsletter between February and April 2017. When a potential case was identified, a standard proforma was used to collect further details to characterise the pre-disposing factors, clinical and biochemical features, response to various management strategies and outcome.

Patients and results:

A total of 10 cases from 6 centres across the UK were collated between November 2016 and July 2017. All cases were associated with use of the AAF, Neocate[®]. Biochemical surveillance had not been instituted in any of the cases prior to presentation. **Table 1** provides details of Neocate[®] feed and treatment and **Table 2** the biochemical features at presentation.

Clinical details at presentation:

Patient 1: Six month old male infant (born 31⁺⁰ weeks gestation) with presumed cow's milk protein allergy (CMPA) was incidentally found to have rickets on a chest radiograph performed during an admission for bronchiolitis.

Patient 2: Ten month old female infant (born 27⁺⁰ weeks gestation) with gastro-oesophageal reflux disease (GORD) and CMPA was referred with bowing deformities of the legs.

Patient 3: Eleven month old male infant (born 33⁺⁶ weeks gestation) with Pierre-Robin sequence, cleft palate and GORD was referred for incidental finding of rickets on a chest radiograph. He had undergone fundoplication for severe GORD.

Patient 4: Eighteen month old female child (born at term) with CHARGE association and GORD was referred for incidental finding of rickets on chest radiographs.

Patient 5: Nine month old male infant (born 31⁺⁰ weeks) with chronic lung disease, severe bronchiolitis warranting tracheostomy, GORD and failure to thrive was referred for oblique fracture of the right femur and rachitic changes on chest radiograph.

Patient 6: A 3 year old female child (born at term) with severe combined immune-deficiency was referred for fracture of the femur and osteopenic bones on radiographs. She was receiving steroids for severe graft versus host disease following bone marrow transplantation.

Patient 7: Five month old male infant (born 34⁺⁴ weeks gestation) with septo-optic dysplasia, GORD, chromosome 8q12.3 deletion and tectal plate glioma was incidentally found to have low serum phosphate and high alkaline phosphatase (ALP) on surveillance.

Patient 8: Nine month old female infant (born 34⁺³ weeks gestation) with CMPA and GORD was referred for multiple fractures and rickets on radiographs.

Patient 9: Eight month old male infant (born 28⁺⁰ weeks) with microcephaly, hypoxic ischaemic brain injury, previous E-coli sepsis and meningitis, poor growth, disordered development and possible cortical blindness was referred due to an incidental finding of 7th rib fracture and osteopenia on chest radiograph.

Patient 10: Fifteen month old female infant (born 25⁺⁴ weeks gestation) with evolving cerebral palsy, periventricular leucomalacia, short gut secondary to bowel resection, GORD, grade 2 retinopathy of prematurity, seizures and dystonia was monitored for ongoing hypophosphataemia and eventually sustained a fracture of the humerus, and rickets was noted on radiographs.

Clinical details following presentation:

Hypophosphataemia was observed in all cases except patient 6 (P6) who was treated with phosphate supplements; P6 also had had a change in formula feed. Hypocalcaemia following phosphate supplementation occurred in three patients (P2, P4 and P9) necessitating calcium supplements and alfacalcidol treatment. Normalisation of serum phosphate, within 1 week to 4 months, was noted in all 9 patients who received phosphate supplements. Patient 10 experienced recurrent episodes of hypophosphataemia when off supplements.

Patients who remained on exclusive Neocate[®] feed experienced disease progression with persistently elevated ALP, long bone deformities (P6), new fractures (P10) or recurrent fractures (P8 and P9) despite phosphate supplementation. Patient 4 who received other feeds in addition to Neocate[®] (50% total parenteral nutrition) experienced ongoing hypophosphataemia and raised ALP without disease progression. When Neocate[®] was stopped, either because it was suspected to have contributed to the hypophosphataemia or HR or changed as per dietetic plan (P3, P4); serum phosphate and ALP normalised. Radiological healing of rickets off Neocate[®] and phosphate supplements was noted in patients (P2, P3, P4 and P8) where a minimum of 6 months follow up data was available. **Figure 1** illustrates rickets on radiographs of patient 2 at presentation and healing at 6 months off supplements following Neocate[®] cessation.

Discussion:

We highlight a rare and preventable cause of hypophosphataemia and HR in children related to the use of the AAF Neocate[®]. HR resulted in significant morbidity including skeletal deformity and fractures. We detail the associated co-morbidities, presenting features, biochemical characteristics, management and outcomes. There was a delay in suspecting Neocate[®] as the causative agent in the majority of the patients described, with some associations made only in retrospect, due to the lack of familiarity with this entity.

A recent report of 51 cases from across 17 centres in the United States describes the association between the AAF Neocate[®] and hypophosphataemia in a large case series [7]. The findings from our cohort confirm that most cases are observed in children born prematurely and had other co-morbidities especially related to the gastro-intestinal system such as GORD. The increased prevalence of hypophosphataemia and metabolic bone disease in preterm infants [9] can lead to a delay in considering Neocate[®] as the causative agent. One patient was noted to have hypophosphataemia shortly after commencing Neocate[®] but this was attributed to prematurity. After 4 months on Neocate[®], osteopenia on radiographs was noted, which again was considered secondary to prematurity, and at 5 months on Neocate[®] presented with fractures.

The absorption of minerals such as calcium and phosphate in preterm infants is reduced [4], hence pre-term formulae are enriched with minerals [10] to ensure adequate mineral supply for growing bones. The bioavailability of calcium and phosphorus from formula milk is less when compared to human milk [11]. Hypophosphataemia has not been associated with other amino acid (Nutramigen Puramino[®]) or extensively hydrolysed formulas (Infatrini peptisorb[®] and Nutramigen[®]), indicating its unique association with Neocate[®]. The Neocate[®] preparations available in the UK have changed over time. The current preparations include

Neocate[®] Syneo and LCP (Long Chain Polyunsaturated fatty acid) for infants and Neocate[®] junior for children aged >1 year, which was previously available as Neocate[®] advance. The phosphorous concentration in Neocate[®] LCP (341mg/100g) is relatively more when compared to other AAF such as Nutramigen Puramino[®] (260mg/100g) or other standard infant formulas such as SMA[®] PRO First Infant Milk (180 mg/100g). Although most patients in our cohort were on the Neocate[®] infant or LCP preparation, a similar association was noted in patients who were on Neocate[®] advance.

The most common indication for Neocate[®] use in our cohort was GORD followed by cow's milk protein intolerance (CMPI). Some patients were implicated to have co-existence of GORD and CMPA/CMPI. GORD is very common, affecting 40% of term infants [12] with a higher prevalence in premature infants which poses diagnostic and management challenges [13]. The reflux symptoms in GORD are often attributed to CMPA/CMPI and a trial of AAF is often initiated despite lack of diagnostic evidence [12]. The National Institute for Health and Care Excellence (NICE) guidelines discourage the use of AAF in GORD [12]. The European Society for Paediatric Gastroenterology, Hepatology And Nutrition (ESPGHAN) recommends a trial of extensively hydrolysed formula (eHF) before starting AAF for proven CMPA [14]. Extensively hydrolysed formulas are also reported to be more cost effective than AAF [15]. One patient was prescribed AAF by the general practitioner for presumed CMPA when presenting with reflux symptoms, which raises the question of whether patients should be reviewed by specialists before commencing AAF.

Proton pump inhibitors (PPI) such as omeprazole and lansoprazole and H₂ receptor antagonists (H₂RA) such as ranitidine are frequently used in the setting of GORD, despite their use being discouraged [12]. The case series from the United States hypothesised that increased gastric pH secondary to antacid use or post-pyloric feed may contribute to altered calcium and phosphate absorption [7]. In our cohort, five patients received post-pyloric feeds,

however two were fed orally. Given that the phosphate content in Neocate[®] meets the recommended allowance [16] it is plausible to hypothesize altered absorption as the causative factor although the exact mechanism contributing to reduced absorption remains unclear.

The clinical presentation included: incidental finding of rickets or fracture with osteopenia on radiographs, clinical presentation of fractures with rickets or osteopenia on radiographs, bowing deformity and biochemical abnormalities alone. One patient sustained a fracture (with rickets noted on radiographs) whilst under surveillance for hypophosphataemia.

Only one patient was diagnosed early with biochemical features of HR (low phosphate and raised alkaline phosphatase with normal calcium and 25 hydroxyvitamin D). Despite the majority of the patients being under follow up in a secondary care centre with dietetic monitoring, the diagnosis was delayed. The duration of Neocate[®] feed prior to presentation in our cohort varied from a minimum of 3 months to a maximum of 15 months and we noted that the longer the duration of Neocate[®] use, the more severe the clinical manifestations were (rickets and recurrent fractures).

Biochemical features at presentation were consistent in all patients with low serum phosphate, raised ALP and normal serum calcium (**Table 2**). Normal values for 25 hydroxy vitamin D and PTH excluded hyperparathyroidism and vitamin D deficiency. When renal TRP was calculated it was normal ($\geq 96\%$) in all cases indicating normal renal tubular function. In the evaluation of patients with HR, in addition to a bone profile, PTH and serum 25OHD levels, it is crucial to collect a paired urine and serum phosphate and creatinine to calculate the TRP. The TRP will be low in causes of renal phosphate wasting but normal or high in Neocate[®] associated HR. The paired samples must be collected before starting any phosphate supplements as this will help distinguish renal phosphate wasting (reduced TRP) from nutritional insufficiency (normal or increased TRP). The manufacturers highlight the

need for biochemical monitoring (6 months after starting Neocate[®] and then annually or more frequently if required) for micronutrient deficiencies in children with co-morbidities. Based on our experience with the above cohort, as a minimum we recommend monitoring serum phosphate and ALP monthly. Currently there is lack of robust evidence to recommend routine monitoring in well children on Neocate[®] in the community. Although a recent study has reported normal mineral status in well children with CMPA on amino acid based formula Neocate[®] [17], the study was limited due to its very short duration of follow up (16 weeks) and lack of bone turnover markers (ALP) for identification of early bone disease.

Primary treatment included phosphate supplementation as with management of any other form of HR [18] apart from one patient who received a change in formula as an association between AAF feed and hypophosphataemia was recognised at an early stage. Hypocalcaemia following phosphate supplementation was noted in three patients necessitating calcium supplementation and/or alfacalcidol treatment. We therefore recommend close monitoring of serum calcium at treatment initiation and encourage the use of alfacalcidol to maximise calcium absorption. Ultimately, all except one patient had a change in formula either due to ongoing hypophosphataemia or as per dietetic plan. Reversal of biochemical and radiological signs of rickets was noted in patients off Neocate[®] and off phosphate supplements with sufficient follow up duration indicating a reversible cause of hypophosphataemia.

Our study is limited due to its retrospective nature. The association of AAF and HR was made in retrospect in two patients. It is difficult to identify definitive risk factors due to the complex medical background of the majority of the children reported here. It is not known whether well children in the community on Neocate[®] for prolonged duration (> 3 months) have biochemical or radiological abnormalities, which warrants further prospective studies.

It is likely that Neocate[®] associated hypophosphataemia is due to poor intestinal absorption of phosphate, which is also supported by reversal of hypophosphataemia following discontinuation of this formula. Healthcare professionals diagnosing and managing GORD and CMPA/ CMPI should be familiar with practice guidelines, the association of AAF Neocate[®] with hypophosphataemia, and adopt close monitoring of children with gastrointestinal co-morbidities as per the manufacturer's recommendations. Management of Neocate[®] associated hypophosphataemia should include change of formula where feasible and phosphate supplementation where necessary.

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Figure 1: Radiographs of patient 2 demonstrating radiological evidence of rickets at diagnosis (a & b) and healing of rickets 6 months (c & d) after stopping Neocate®.

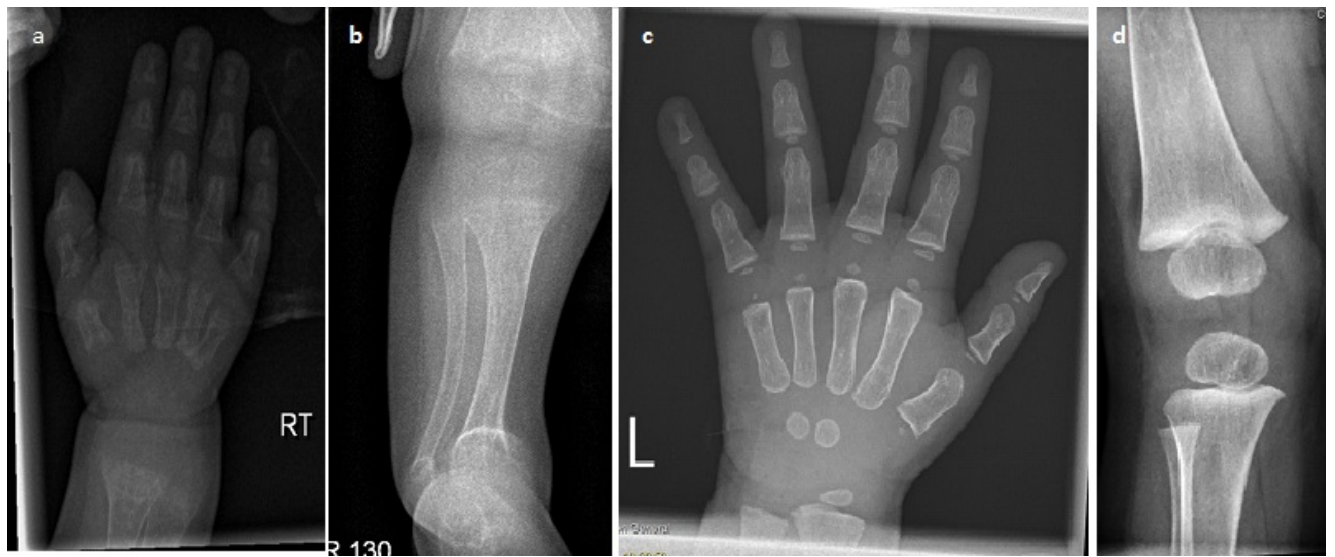


Table 1: Feed specifications and indications; and treatment on all patients are detailed below. Abbreviations used are indicated below the table.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Presentation age (months)	6	10	11	18	9	36	5	9	8	15
Type of formula	Neocate [®] LCP	Neocate [®] LCP	Neocate [®] LCP	17% Neocate [®] LCP	20.7% Neocate [®] LCP	Neocate [®] LCP then Neocate [®] advance	Neocate [®] LCP	Neocate [®] LCP	Neocate [®] LCP	Neocate [®] LCP+ junior
Neocate [®] indication	Presumed CMPA	GORD, CMPI	Severe GORD, lactose intolerance	GORD	GORD, failure to thrive, family history of CMPA	Refusing feed, milk, egg, wheat, soy free diet	Severe GORD. Suspected CMPA	CMPI	CMPI	Short gut, GORD
Route of Feed	Oral	Oral	NJ and then gastrostomy	Gastrostomy	NG and then NJ via gastrostomy	NG and oral	NJ	Gastrostomy	NG and then NJ	NJ
Exclusive Neocate [®] pre diagnosis	3 months	10months	8months	>6 months	5 months	15 months	5 months	7.5 months	8 months	11 months
Antacid use	No	Yes Lansoprasole	Yes Omeprazole	Yes Lansoprazole	No	Yes Lansoprasole	Yes Lansoprasole	Yes Omeprazole Ranitidine	Yes Ranitidine	Yes Omeprazole
Neocate [®] stopped as part of treatment	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No
Phosphate supplements	Yes, 2 months	Yes, 3 months	Yes, 14m	6 days; stopped as hypocalcaemic	Yes	Yes	No	Yes, 6 months	Yes	Yes, on and off for 1 year
Additional treatment	Alfacalcidol and Vitamin D3	Calcium supplements	Vitamin D3	Vitamin D3 and Calcium supplements		Bisphosphonate (x1 infusion)			Alfacalcidol and Calcium supplements	Calcium supplements and Vitamin D3

LCP= Long Chain Polyunsaturated fatty acid, CMPA= Cow's milk protein allergy, GORD= Gastro oesophageal reflux disease, CMPI= Cow's milk protein intolerance, NJ= Naso-jejunal, NG= Nasogastric, ALP= Alkaline phosphatase

Table 2: Biochemical features at presentation

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Serum calcium mmol/L NR 2.2-2.7	2.46	2.52	2.6	2.28	2.57	2.47	2.38	2.51	2.21	1.89
Serum phosphate mmol/L NR 1.3-2.4	1.23	0.68	0.83	1.04	0.84	1.34	0.63	0.7	1.04	0.6
Alkaline phosphatase IU/L NR 105-420	1000	1000	3469	431	1653	419	2206	906	2241	1024
Parathyroid hormone NR 10-65 ng/L	24	19.8	17	54	21	31	Normal	9	14	16.5
25 hydroxy vitaminD nmol/L NR >50	59.7	86	88	347	76	131	110	73	106	33
1,25 dihydroxy vitamin D pmol/L NR 20-120	>250	-	>250	-	-	-	-	454	336	-
Tubular reabsorption of phosphate NR >80%	99.7%	-	99.8%	97%	-	-	-	96%	96%	96%